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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,505	11/12/2003	Kenji Kawada	0032-0280P	4761

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,505	KAWADA ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/214,277.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

8.00 8.00

DETAILED ACTION

Applicant's election with traverse of Group I, claim 9, namely terphenyl compound of formula II' in Paper file on 2/15/2005 is acknowledged. Election of species of example I-1327 is also acknowledged. Addition of new claim 10 is also acknowledged.

Claims 1-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The traversal is on the ground(s) that there is no undue burden to search and consider the present claims in their entirety. This is not found persuasive for the following reasons.

First of all, applicants' assertion that there is no search burden apparently stems from the lack of understanding of the search process and different databases to be searched. As recited claim 1 relates to compound of undefined structure with immunosuppressant property. One needs to search not only in-house Patent database EAST and commercial database CASONLINE and others for Non-Patent literature.

Since claim 1-8 lack a defined structure, a structural query cannot be designed for CASONLINE or EAST. Searching a "compound and immunosuppressant" as

keywords in CASONLINE would result in millions of hit. Such search would be not only a serious search burden but would also drain all resources as this dat base is expensive and charges for each reference found. For example there are several immunosuppressants (such as cyclosporine, steroids, thalidomide and others to name a few) currently known and in clinical use and CASONLINE would definitely pick all studies using such compounds.

Searching EAST also require a structure which can be classified and then searched. In absence of a defined structure in claims 1-8, one needs to rely on key word search which would lead to large number of hits for reasons stated above. Furthermore, a compound as recited can be any compound including inorganic compound and without knowing the exact metes and bounds, it would be a serius search burden as these compounds are to be classified in various classes and subclasses and then to be searched.

Secondly, as noted in the previous office action, Group I and Group II are directed to dissimilar compounds with varying cores such terphenyl vs undefined structural cores Group I and II require mutually exclusive search if a thorough search is intended. Classification of Group I is controlled by terphenyl core and functional substituents core hence searching in elected Group I, classes 560, 562, 564 or 568 and their subclasses would not lead to any compound with immunosuppressant property. Each class/subclass has to be searched in East or West. It is mandatory. There is serious search burden as several classes and subclasses are to be searched.

Furthermore, specification has no identified any compound other than terphenyl compound. In that sense, a compound is a compound irrespective of its attributes. Hence it should be noted that as recited the invention of claims 1-8, which are compound claims, urges one trained in the art to identify compounds with the functional attributes recited therein and then deem that compound of instant invention.

Thirdly, applicants have not submitted evidence or identified such evidence now of record showing the terphenyl core and all other cores of Group II to be obvious variants or clearly admitted on the record that all core groups embraced in the instant inventions are equivalent. In which case, examiner needed not search all cores. A prior art which anticipates any one of the groups embraced by a specific core (i.e. choices of I or II) may then render the other core group an obvious variant. In other words, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

In want of such assertion or evidence, searching the entire cores would be serious search burden.

The requirement is still deemed proper and is therefore made **FINAL.**

Claims 9 and 10 under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts does not reasonably provide enablement for making hydrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

Factual Basis:

1. Specication has no working example of hydrate of compound of formula (I') even though nearly 2500 compounds out of millions of compounds embraced in the claim 9 were made and were in contact with water. Yet they have not formed hydrate as evident form spectral data provided for these compounds.

2. Searching the pertinent art in the related terphenyl area did not result in support for such hydrates of terphenyl compounds. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area. Since water is also a solvent, lack of predictability applies to hydrates The scientific basis is clearly evident.

Based on these two facts, the following scope of enablement rejection using relevant Wands factor.

Hence, examiner had clearly met the burden of establishing the prime facie case.

Scope of enablement rejection:

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors

include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to selective immnuosuupressor of IgE production compound of formula I" , or a pharmaceutically acceptable salt or hydrate thereof. Specification is not adequately enabled as to how to make hydrate of compounds of formula (I") Specification has no example of hydrate of the instant compounds. Specication on pages 5, 6, 9, 18 and 33 recites hydrate thereof but there is no enabling of such compounds.

The compound of formula I" embrace terphenyl compounds i. e. a phenyl group linked to two more phenyl groups in the 1, 4-position. The phenyl groups are substituted with R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} along with X-Y group on the para position of one of the terminal phenyl group.

Careful calculation of the number of compounds embraced in the instant formula (I") shows a large number of compounds.

Treating lower alkyl as 1 to 6 carbon atoms, cycloalkyl as 6 choices , aryl as six choices and heterocyclyl as 6 choices and ignoring optional substituents on these groups, X choices will have 17 choices, Y will have 67 choices. Thus the X-Y choices it self will encompass 17x 67 variations.

As for each R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} which amounts to thirteen groups, the various substituents is indeed large. For example each of the variables has approximately using the above guideline of X, Y choices, would result in at least 97 choices and there are thirteen of them and there thirteen position for a mono substituted terphenyl bearing X-Y group. This amounts to 17x67x97x13= 1,436,279 compounds. Of course, this number is an approximation at best as cycloalkyl, aryl and heterocyclyl groups are limited to 6 choices and optional substituents are ignored. Similar extension of the calculation for di, tri, tetra, penta, hexa, hepta, octa, nona, deca, dodeca, dodideca and dotrideca would add large number of compounds to the above number compounds. Thus the genus embraced in the claim1 is large and there is no teaching of any hydrate of this large genus.

Search in the pertinent art, treating water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the

stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. In the instant case of hydrate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates is also applicable to water.

2. **The predictability or lack thereof in the art:**

Hence the hydrate as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to hydrates. There is no example of hydrate of instant compound. Nearly 2500 compounds were shown in the specification each of which has come in contact with water but there is showing that instant compounds formed hydrates. Hence it is clear that merely bring the compound with water does not result in hydrate and additional direction or guidance is needed to make them Specication has no such direction or guidance.

4. **The presence or absence of working examples:**

There is no working example of any hydrate formed. The claims are drawn to hydrate, yet the numerous examples presented all failed to produce a hydrate or even solvate. These cannot be simply willed into existence. As was stated in Morton

International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that hydrates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that hydrates of these compounds exists and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specication has no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired hydrate of the compound of formula I. As noted above, the genus embraces over million compounds and hence the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired hydrate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright,

999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9 and 10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37, 40, 52, 56, 57, 75 and 76 -59, 74 and 76 of copending Application No. 09/214,277. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claim is also embraced in the copending earlier filed application 09/215,277. Note claims 40, 56-57 and 76 embrace the same immnosuppressor composition while claims 37, 52 and 75 embrace a pharmaceutical compostion. A pharmaceutical composition is a pharmaceutical composition irrespective of its intended use or desirable property. Claim 9 and 10 are composition claims with some attributes to the compound. These attributes do not

change the composition and make it different from the composition of 37, 40, 52, 56, 57, 75 and 76 of copending Application No. 09/214,277.

See Intirtool, LTD. V. Texar Corp., 70 USPQ2D 1780. Note court held that " In general, a claim preamble is limiting if recites essential structure or steps or if it is necessary to give" life, meaning, and vitality to claim.'.... However, if the body of the claim describes a structurally complete invention such that deletion of the preamble phrase does not effect the structure or steps of the claimed invention,' the preamble is generally not limiting unless there is clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art.""

Instant claims are composition claims and is clearly defined by a structure namely a terphenyl core with a side chain bearing specific substituents. Omission of the attributes to the composition of the compound of genus of claim 9 or claim 10 would not alter the structure of these compounds and hence the composition .

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 9 and 10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending Application No. 10/704,876. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claim is also embraced in the copending earlier filed application 10/704,876. A pharmaceutical composition is a pharmaceutical composition irrespective of its intended use or desirable property. Claim 9 and 10 are composition claims with some

attributes to the compound. These attributes do not change the composition and make it different from the composition of claims 1 and 2 of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (571) 272-0674. If Applicants are unable to reach Mukund Shah within 24-hour period, they may contact James O. Wilson, Acting-SPE of art unit 1624 at 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

5/12/2005